

Review paper

Phytonutrients and Technological Development in Formulations

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ABSTRACT

Phytomedicines are used by humans since ancient civilizations and is now considered as an important part of traditional and alternative system of medicine. In recent time, phytomedicines have gained special attention based on the fact that a number of current medicines are derived from plant source. Phytochemicals exhibits lesser side effects and are potentially strong therapeutic agents. The global market for herbal drugs is increasing day by day. It has gained widespread acceptance due to its efficacy, accessibility, minimum toxicity, and cost effectiveness. However, solubility, stability and bioavailability are some of the major hindrances in the commercialization process of phytomedicines. Nanotechnology have been potentially productive in improving the solubility, stability, bioavailability, and bioactivity of phytomedicines. Development of nano-phytomedicines or attaching phytomedicines with polymers and modifying their surface properties and permeability have altogether influenced the bioavailability of phytochemicals. Novel formulations like solid lipid nanoparticles, micelles, niosomes, dendrimers, nanotube, liposomes, nano-emulsions nanospheres, phytosomes etc. Have been developed loaded with phytomedicines and have shown extraordinary result. This chapter extensively reviews phytomedicines based novel drug delivery systems having potential activity in different diseases like metabolic disorders, cardiovascular disorders, neurological disorders, viral diseases, cancers, inflammatory diseases and wound healing and lastly future prospect is discussed.

Keywords: Nanophytomedicine; Phytonutrients; Novel drug delivery system; Cancer; Neurological disorders; Diabetes; Viral disease; Inflammatory disorders; Wound healing

Introduction

Phytomedicines or herbal medicines can also be termed as phytonutrients, are active compounds derived from natural sources. Throughout the history of mankind numerous ancient literatures can be found related to the use of phytonutrients or phytomedicines in the form of

single entity or mixture of herbal compounds as remedies for many diseases. Since the ancient times humans were clear about using herbs and plants for treating their illness, but the exact mechanism of action was unknown to them. Knowledge accumulated

through years of experience, humans slowly began to understand traditional medicines in a better way and started to categorize phytomedicinal herbs into groups according to their effects on different diseases. Further, the knowledge of biomedicines and the chemistry involved in it brought new understandings about the active ingredients involved in phytomedicines and their possible mechanism of action [1].

One of the oldest literatures which enlist medicinal plants, minerals and animals is Sheng-Nongs Herbal book dated back to 3000 B.C. The book discusses about 365 plants [2]. Even today phytomedicines are used directly or indirectly in the mainstream medicinal system. Traditional way of treatment stands as the largest practiced medicinal system around the globe. The great Himalayan ranges encloses four mega medical traditional systems, namely: The Chinese system of medicine, the Ayurvedic system of medicine, the Tibetan medicines, and the Unani system of medicines [2]. Ayurvedic system of medicine is one of the oldest and most widely practiced traditional system of medicine with its own pharmacopoeia enlisting details of about 1000 plants. There are several registered ayurvedic practitioners in India, Sri Lanka, Nepal and other neighboring countries [3]. In China, herbal medicines have expanded enormously over the years. Their current inventory of herbal medicines enlists more than 11000 herbs which includes both cultivated and wild forms of plants. The ancient knowledge from Ayurvedic and Chinese system of medicines has been passed on to generations in revised versions. However, currently only Chinese system of medicine is constantly updating their inventory of tradition herbs for different ailments. Similar efforts have also been initiated in India which can be considered as a great move. The government of China is the most active body among other countries of the world in terms of blending the traditional system of medicine with the modern allopathic medicinal system. The traditional herbal medicines reached a bit late to Europe from its Asian counterparts. In Europe it was first originated in Ancient Greece and was based on the accumulated knowledge of herbal medicines [4] from Babylon, Egypt, and Persia at around 5th century B.C. [5]. *De Materia Medica* by Dioscorides can be considered as one of the most influential books in the history of herbal medicines, as it was considered as a standard text for the practitioners of the West for almost 1500 years. During the same era, Galen prepared more than 125 antidotes which included more than 100 herbs and other medicinal substance. These preparations were later known as Galenical's while the system of preparation and complex procedures came to be known as galenic system. This

gave physicians the ultimate authority in the medical system and the herbal formulators began to be side-lined in Europe. However, the traditional herbal medical system was survived by Catholic monks during the Middle Ages. The physicians from Arab conducted extensive research on medicinal herbs of India, Persia, Europe and other regions of Asia. With the discovery of America as the New World, many medical herbs were introduced to Europe and Asia [6]. Treatment by medicinal herbs kept on being the mainstay of health care system in the western world. But with the accidental synthesis of Urea in the 19th century brought an urge for developing synthetic compounds which eventually lead to the downfall of the herbal medical system. And its practice became confined to only some regions of Asia.

During the recent time, herbal medicines or phytomedicines are again gaining popularity among people due to the major side effects caused by synthetic chemicals. For the better understanding of herbal medicine Ernst categorized them into three groups: Traditional herbalism, over-the-counter herbal medicine and phytotherapy [7]. In phytotherapy scientific studies are conducted to produce data upon which their pharmacological activity depends. This further gets standardized before being applied to any distinct clinical condition. Phytotherapy in many means follows the same principles of pharmacotherapy and requires knowledge and skill for its development, and application for treating any disease [8]. On the other hand, traditional herbalism does not provide any scientific data and usually involves concoction of different plant extracts based on the disease and characteristic of the patient [9]. In a study by Guo et al., the researchers failed to conclude with convincing evidence to support the use of individualized herbal medicine for any specific indication [10].

Modern natural research on phytomedicine gained popularity after the isolation of morphine from opium poppy. Currently the understanding of phytomedicines has enormously evolved, which now stands as an interdisciplinary area of science dealing with all aspects of isolating the phytochemicals, characterization of the chemicals, formulation into a potent delivery form and its biological activity. Such active compounds are generally referred to as secondary metabolites which includes alkaloids, steroids, phenols and terpenoids. Although phytomedicines have great therapeutic value, their use is limited due to low solubility and bioavailability. Some phytonutrients were found to be possessing toxicity and most of them encounter stability issues which severely hampered their use a drug [11].

The market of herbal products globally is expected to reach USD 411.2 billion by the year 2026 and is expected to grow at a CAGR of 20.5% from 2020-2026 [12]. Now a days more people are turning towards organic foods and natural/herbal way of treatment for various diseases. The current scenario suggests the need for extensive data on the safety, efficacy, and toxicity profile of herbal medicines [13]. Toxicity by herbal medicines and the level of seriousness is varied depending upon the type of herbs consumed. Combining herbal medicine with the conventional system medicines is another area requiring special consideration. Type of disease, route of application is some of the factors which influence the dosage form of herbal medicines. Formulating herbal medicines into pharmaceutical dosage forms to provide accurate dose is one of the key factors which effects the commercialization of herbal products. Safety, toxicity, and efficacy are influential factors which limits the commercialization of herbal products.

To formulate herbal drugs into a potential dosage form is quite tedious and difficult owing to their poor solubility profiles. Novel drug delivery system provides an innovative platform to develop herbal medicines into potent dosage forms [14]. The ideal drug delivery system is capable of drug targeting and also provides control over the release of the drug from the formulation and reaches optimum therapeutic effect while causing minimum side effects. Nano formulation-based delivery system are being extensively researched during the recent times. Nano-phytomedicines developed by combination approach of nanotechnology with herbal medicine. Herbal powders or their extract shows impressive result during in-vitro studies but there in vivo reports quite poor due to their low solubility, poor absorption, low bioavailability and rapid clearance etc. Nanotechnological approaches like phytosomes, nanospheres, liposomes, niosomes, are being continuously studied to improve the delivery of herbal drugs [15].

Nanotechnology have been found to be potentially effective in improving the bioactivity and bioavailability of herbal drugs. Novel methods for developing formulation of herbal medicines includes: (I) Reducing the particle size to nano level [16], (II) Addition of specific polymers with phytomedicines [17] (III) Extension of nano-structured carrier systems for phytomedicines [18] and (IV) Modification of the surface properties of phytomedicines [19]. These modifications are achieved by coating the phytomedicines with hydrophilic or mucoadhesive polymers or surfactants. These alterations modify the

zeta potential of nanoparticles leading to improvement in the particle uptake and stability of the system [19]. Several reports suggest improved biological activity and therapeutic potential of nano-phytomedicines that conventional formulations.

This chapter focuses on phytomedicines, its history and nanotechnological approaches to enhance their solubility, bioavailability, and bioactivity. Further the chapter discusses about the phytomedicines based novel drug delivery systems for different diseases like inflammatory and bowel diseases, cardiovascular disorders, neurological disorders, cancer, viral disease, metabolic disorders etc. Lastly concluding remarks and future perspective in this field is presented.

Novel technological approaches in the development of phytomedicine based delivery systems

Phytomedicines are getting popular day by day and scientist are involved in developing more potent and targeted drug delivery systems for them. But these phytomedicines comes with certain limitations. Since the phytomedicines are secondary metabolites and are produced in exceptionally low quantity and their screening possess another challenge. Processes like identification, isolation and fractionation are also hectic and tedious process. Many of the phytomedicines show extraordinary results during in vitro studies but there in vivo activity is reported to be very ordinary owing to their poor solubility, low absorption and consequently their bioavailability. Phytomedicines are also reported with structural instability which may result in biotransformation and rapid clearance leading to premature drug loss. Currently scientists are showing special interest in nanotechnological approach for developing novel drug delivery system [20]. Nanotechnology is an effective tool that can be exploited to effectively eradicated the before mentioned limitations. Nanophytomedicines can modify surface properties, their solubility profile and improve their permeability through the biological membrane. Novel technologies like niosomes, liposomes, phytosomes, nanospheres etc are capable of delivering phytomedicines to the targeted site. Incorporating herbal drugs into such systems potentially increases the solubility, stability, therapeutic activity, and distribution while decreases toxicity profile and chemical degradation [21]. Exploitation of nanotechnology enhances the delivery of phytomedicines with poor aqueous solubility, provides targeted delivery system, efficient delivery of macromolecular phytomedicines into intracellular sites, co-delivery of multiple phytomedicines and as theranostic agent by incorporating a bioimaging agent

with phytomedicine [22]. Different nanotechnological approaches like liquid crystals, polymeric nanoparticles, liposomes, solid lipid nanoparticles, microemulsions etc. are potent approach in developing novel phytomedicines based delivery systems (**Figure 1**).

Nanostructured carriers and solid lipid nanoparticles

Solid lipid nanoparticles [SLNs] were first developed in the 1990s as the colloidal carrier system which provided better physiochemical stability and improved protection of labile drugs from getting degraded [23,24]. The lipids make up the purified triglycerides which further makes the solid lipid nanoparticles and are stabilized by the addition of surfactants [25]. SLNs have solid lipid matrix which protects drug molecules from chemical degradation. However, crystallization may occur in during production which may lead to poor

encapsulation efficiency and eventually low drug release [24]. Formulation of SLNs is done by adding oil (lipid) to o/w emulsion which contains solid lipid or a mixture of lipids promoting its formation [26]. Owing to their small size SLNs can be administered via percutaneous, parenteral, or oral route [27]. Nanostructured lipid carriers [NLCs] provide the advantage of higher encapsulation efficiency and minimizes loss by expulsion during the encapsulation process. These systems are being considered for colloidal drugs as an alternative vehicle [24]. They are a disorganized liquid matrix containing mixture of both solid and lipid phases which can accommodated active ingredient. They can be administered through dermal, pulmonary, oral and intravenous routes. SLNs and NLCs are produced by exploiting different techniques like microemulsion, high pressure homogenization, emulsification evaporation and emulsification sonication techniques.

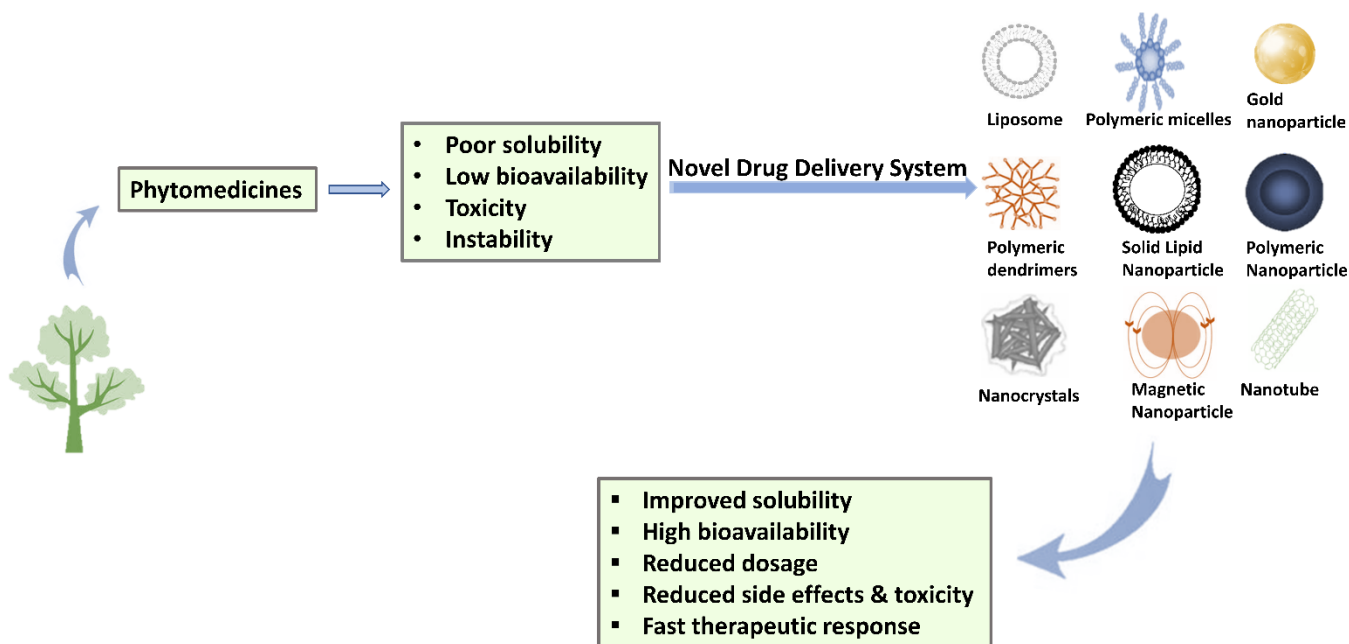


Figure 1: Advantages of encapsulating phytomedicines into novel drug delivery system.

Liquid crystals

These are condensed structures having intermediate phase between isotropic liquid and crystalline solid having an ordered or disordered orientation. These are mesophasic structures mostly having cubic or hexagonal structures and are characterized into thermotropic and lyotropic liquid crystals. In thermotropic liquid crystals, liquid crystals convert to isotropic liquid at a specific temperature. On the contrary functional micellar units make up the lyotropic liquid crystals. They are amphiphilic molecules which

have a concentration dependent mesophasic formation [28]. Optical isotropy of mesophasic structures are determined by electron microscopic technique with cryofracture, polarized light microscopy, neutron diffraction [29]. Liquid crystals have numerous applications in the pharmaceutical industry owing to the stability and ability to effectively encapsulated bioactive compounds which are prone to inactivation or degradation upon interaction with lipid membranes. Liquid crystals can deliver drug at the target site and facilitate interaction between cell membrane of the active site and drug molecules further assisting its entry

and eventually pharmacological response [30]. Phytomedicines can be incorporated into liquid crystals. Vegetable oils are widely used in developing liquid crystals due to their low occlusive property which allows better skin penetration and high loading of drug [31].

Polymeric nanoparticles

Polymeric nanoparticles are made up of biocompatible and biodegradable polymers which have the ability to release drug in a controlled and targeted fashion [32]. Polymeric nanoparticles also increase the solubility of its constituents and eventually leads to decrease in dose and improves the absorption of therapeutic agent. They are mostly non-immunogenic, non-thrombogenic, non-toxic, non-inflammatory, do not react with neutrophils and bypass the reticuloendothelial system. Polymeric nanoparticle is capable of drug targeting to special tissue or at cell surfaces [33]. The polymers used in the development of nanoparticles can be of artificial, natural or biodegradable nature. However, natural materials are preferred in their formulation due to their ability to encapsulate more than one constituent, sustained releases, improved residence time and low side-effects [33]. Polymeric nanoparticles can appear as either nanospheres or nanocapsules. Nanospheres are made up of polymeric structure on which active constituent is adsorbed or retained. On the other hand, in nanocapsules, polymeric structure surrounds an oily core. The active therapeutic agent can be dissolved in the oily central core or adsorbed in the polymeric membrane [34]. Methods like in situ polymerization or precipitation techniques are used to prepare polymeric nanoparticle system. These systems come with the disadvantage of precipitation and physicochemical stability which can be overcome by employing dehydration, sublimation, and drying techniques [34].

Liposomes and Phytosomes

Liposomes are vesicular systems in which aqueous system separates two or more concentric lipid bilayers. The aqueous system encapsulates hydrophilic substance while lipophiles are inserted in the membrane side. For lipophilic systems aqueous phase makes the membrane side while the lipophilic substance is encapsulated in the lipid bilayer membrane. Natural or synthetic phospholipids, antioxidants and sterols makes up these vesicles [35]. Thin film dispersion stands among the most unique technique for formulating liposomes, which is based on Bangham's method [36] and involves three steps: Firstly, the lipid is dissolved in organic solvent, which is then evaporated to form a thin film, the process is followed by the addition of the aqueous

media into lipid film to form liposomal suspension. However, the method comes with the drawback of producing multilamellar large vesicles having low encapsulation efficiency. In the recent times, several other techniques like ultrasonication, freeze-thawing, extrusion homogenization to further process the liposomes obtained from thin film technique. These techniques help in improving the stability and provides higher encapsulation efficiency and also produces more homogeneous liposomal products. Nanoliposomes from liposomes are prepared by evaporating methanol/chloroform from the solution of amphiphilic contents like carbohydrate sterol, phospholipids, protein derivatives etc. On adding hydrophilic contents to the thin film layer which is followed by the addition of the water loving compound with applying sufficient amount energy in the form of agitation or shaking, thermal energy, sonication forms bilayer sheets with the inclusion of water hating compounds which can be separated from the bulk to give nanoliposomes [37-39]. Nanoliposomes can also be formed by entrapping the compound during vesicle formation where the hydrophobic compounds are encapsulated in the lipid while hydrophilic compounds are located in the aqueous part in the bilayer system [39,40]. Liposomes are also being exploited in the nutraceutical and food industries.

Phytosomes are novel formulations encapsulating phytonutrients and are capable of providing enhanced absorption and improved bioavailability compared to standard herbal extracts [41]. The major interaction which occurs in the phytosomal platforms is interaction between the phytoconstituents and phospholipids, which is also known as phyto-phospholipid interaction. This interaction produces lipid and aqueous soluble complexes which make them a unique delivery system. Phytosomal technology has efficiently improved the bioavailability of many plant extracts like silymarin [42], curcumin [43], green tea, grape seed, olive oil and ginseng polyphenols [44] ginkgo biloba [45]. Thus, this technology could provide an alternate platform for designing and producing novel phytonutrient-based delivery systems.

Microemulsions

Microemulsions was introduced in 1943 as fluidic system which are transparent emulsions in which water is dispersed in oily phase or vice-versa. It also contains surfactants with or without a cosurfactant. These systems are thermodynamically stable. The active constituents can be entrapped in the aqueous or oil phase [46]. Microemulsions acts like reservoirs, as the drug separates from the dissolution medium their release is controlled by membrane enclosing it. These

systems are capable of connecting different groups of molecules and thus modulates their solubility, stability and eventually their bioavailability [46]. These systems also provide prolonged actions, drug targeting and modified systems with varying degree of lipophilic/hydrophilicity with one system [47].

Solid dispersions

Solid dispersion can be stated as a dispersion system containing one or more active ingredient in an inert carrier or matrix at the solid state prepared by different methods [48]. The drug molecule can be dispersed as crystalline or amorphous particles or as separate molecules, while the carrier can be in the amorphous or crystalline state. Solid dispersions have been reported to improve solubility and dissolution of poor aqueous soluble drugs. These advantages were achieved by reducing the particle size, improving porosity and wettability, and changing the state of drug particle from crystalline to amorphous state. [49]. Depending on the physical state of the carrier the solid dispersions can be broadly classified as amorphous solid dispersions or crystalline solid dispersions. Based on the composition, the solid dispersions can also be classified into four generations. The first-generation solid dispersions were crystalline in nature and comprises of urea [50] and sugars such as mannitol and sorbitol [51]. The urea-based solid dispersions were found to exhibit enhanced solubility in organic solvents and water. The second-generation solid dispersions comprised of amorphous carriers which were mostly polymers of natural or synthetic origin. The molecular weight of polymers influences the selection of a polymer as a carrier. The third-generation solid dispersions were developed with the addition of self-emulsifiers or surface-active agents as carriers. Significant improvement in the solubility and drug release rate were reported and complications like recrystallization and precipitation were controlled. These surfactants are used as additives or process aids which were found to enhance the biopharmaceutical performance of the supersaturated systems. The fourth-generation solid dispersion are controlled release solid dispersion (CRSD) encapsulating poorly aqueous soluble drug with a short biological half-life. Controlled release solid dispersion of poorly aqueous-soluble drugs enhances solubility and provided extended release in a controlled manner. Solid dispersions can be prepared by exploiting various methods like microwave irradiation, Cryogenic processing techniques, Spray drying, Coprecipitation method, Electrostatic spinning, Supercritical anti-solvent technique, Hot melt extrusion and Meltrex™ and melt agglomeration.

Nanoemulsions and self-nanoemulsifying drug delivery systems

Nanoemulsions are comprised of nanosized droplets with diameter typically ranging between 20-200 nm [52]. Nanoemulsions are heterogenous and transparent dispersions of two immiscible liquids which are thermodynamically at non-equilibrium state [53]. These are kinetically stable systems because of extremely slow destabilization rate [54]. Their bioavailability enhancing ability were reported almost four decades ago. These systems are also referred to as “Approaching thermodynamic stability” system as their fine particles prevents sedimentation or creaming, coalescence or flocculation due to Brownian motion, and non-deformity of the droplet [55]. Although nanoemulsions are comparatively stable systems still they are prone to breaking via “Ostwald ripening” which arises due to the polydispersity issues [36]. Factors like hydrolysis of drugs, poor palatability, greater water content and long-term storage limits their application [56]. The emergence of spontaneously nanoemulsifying drug delivery system has promisingly restored the prominence of nanoemulsions to a greater extent.

Self-nanoemulsifying drug delivery systems have emerged as a promising delivery system for the efficient delivery of poor aqueous soluble drugs [57]. Self-nanoemulsifying drug delivery systems are well established technique for improving the solubility and absorption of the lipophilic drugs [58] which is achieved either by decreasing the size of oil droplets or increasing the surface area and by incorporating it into mixed micelles that can easily pass through the intestinal lumen [59]. Self-nanoemulsifying drug delivery systems have distinctive features like palatability, patient compliance, long term stability, ease of formulation, reduction in dose, and scale-up synthesis which make them superior delivery systems in comparison to conventional micro and nanoemulsions. Self-nanoemulsifying drug delivery systems were also found to reduce cytochrome-P450 metabolism in gut enterocytes, improve oral bioavailability, enhance lymphatic transport via Peyer-patches, and protect against the first pass metabolism [59]. Self-nanoemulsifying drug delivery systems can be categorized into solid-self-nanoemulsifying drug delivery systems and liquid self-nanoemulsifying drug delivery systems. The solidification in these systems is achieved through melt granulation, adsorption on inert solids like lactose, microcrystalline cellulose, aerosol etc. and spray drying technique [60].

Polymeric and lipid micelles

Polymeric micelles are nanocarrier systems which are formed by the arrangement of amphiphilic block copolymers in aqueous solutions. These systems consist of a hydrophobic core which assists in encapsulating hydrophobic drugs and a surrounding hydrophilic shell. Polymeric micelles assist in the effective delivery of therapeutic, imaging, and diagnostic agents. They exhibit numerous favourable properties like enhanced stability, increased biocompatibility, capability to solubilise variety of sparingly soluble drugs, capacity to modulate the release profile of the entrapped therapeutic agents and the ability to accumulate at the target site [61].

Formulating lipid micelles is a common approach to increase the bioavailability of drugs with low solubility. The lipo-solubilization capability of phospholipids facilitates membrane permeation which eventually improves the bioavailability of drugs. Phospholipids are amphoteric in nature and are an integral component of the cell membrane thus they enable drugs to be easily absorbed. Lipidic micelles is gaining popularity for being effective in enhancing solubility and bioavailability of lipophilic drugs. Their nanometric size assist in oral absorption due to the presence of Peyer's patches and M cells in the intestine [62].

Dendrimers

Dendrimers are synthetic complexly branched macromolecule ranging within nanometer dimensions. It consists of a central core, surrounded by dendritic branches, and an outer surface with surface functional groups. Therapeutic agents can be encapsulated or conjugated either inside the core or at the surface which makes them an attractive carrier for phytomedicines especially which have anticancer therapeutics [63]. Drug encapsulation within dendrimer branches can off undesirable controlled release properties for phytoconstituent with anticancer effect. Polyglycerol dendrimers of paclitaxel has been reported with improved solubility in water and enhanced bioactivity [64].

Inorganic nanomedicines

Inorganic nanoparticles have been extensively studied due to their versatile development strategies, unique physico-chemical properties, outstanding biocompatibility and easy surface engineering which could assist them in being a potent delivery system for phytonutrients. Recent advances in inorganic nanoparticles, includes gold nanoparticles, magnetic nanoparticles, carbon nanotubes [65].

Gold nanoparticles

Gold nanoparticles are used in different scientific domains, of which the biomedical field is most extensively using gold nanoparticle system for effective delivery of therapeutic agents and phytonutrients. They have favorable properties like improved stability, excellent compatibility, low toxicity, and possibility of interaction with a variety of substances for controlled drug delivery of phytonutrients. Furthermore, owing to their large surface area and the ability of being conjugated with a large variety of phytonutrients and therapeutic agents, gold nanoparticles have potential of carrying phytonutrient based anticancer agents [66].

Magnetic nanoparticles

Magnetic nanoparticles have been extensively studied for diagnosis and treatment of cancer using phytonutrients. Due to their outstanding magnetic properties, biodegradability and biocompatibility, magnetic nanoparticles have become the most considered novel delivery system for encapsulating phytonutrients. Magnetite nanoparticles can be used directly or dispersed in the lipid or polymeric matrix as cores, and they appear to be extremely suitable for phytonutrients and chemo-therapeutic drug delivery. In fact, they can be prepared in diverse sizes and can be functionalized by surface modification to carry various plant molecules like curcumin [67].

Carbon nanotubes

Scientist have shown more interest in carbon nanotubes in past two decades due to their unique structure and physicochemical properties like large surface area and aspect ratios, easy surface modulation, and stability in the nanoscale range. They are attractive nanocarrier system for phytomedicines based cancer treatment [68]. Many phytosomes based like betulinic acid conjugated oxidized multiwalled carbon nanotubes have been developed and were found to improve efficiency of phytochemicals against cancer cell lines with reduced toxicity [69].

Novel drug delivery systems of phytomedicines for metabolic/cardiovascular diseases

Metabolic syndrome is a health disorder that causes a series of serious medical conditions. These risks include obesity, hypertension, insulin resistance, atherosclerotic disorders, and other cardiovascular disorders [70,71]. Lifestyle modifications along with medical treatment is often referred. Usually, the prescribing pattern includes lowering of blood pressure and blood glucose and

triglyceride level. However, treatment with common medication includes side-effects specially after long term application. Nanoformulation of phytomedicines is a novel approach in this regard. These nano vehicles provide the advantages of improved bioavailability and solubility of drug, decreased side effect, prolonged circulation time and targeted action of drug [72]. Phytomedicines like resveratrol, emodin, curcumin, capsaicin, emodin, silybin, baicalin, quercetin, oleoresin is extensively studied. These phytoconstituents have been encapsulated into different nano systems like liposomes, micelles, solid lipid nanoparticles, lipid carriers and others [73]. In comparison to conventional formulations, nanoformulations provides the advantage of targeted drug delivery, improved bioavailability, better surface to volume ratio, sustained and controlled release modifications. However, these nanoformulations also comes with the disadvantage of instability, poor shelf-life, toxicity and are more expensive than conventional medicines [74].

Multipolymer nanoparticles of phytomedicines provides a promising platform to improve aqueous solubility and bioavailability of poorly soluble phytoconstituents. Curcumin has poor aqueous solubility [75]. Curcumin loaded multipolymer nanoparticles has been reported to have a positive effect on relieving diabetic cardiomyopathy. The multipolymer encapsulation of curcumin affects diabetic cardiomyopathy and also cross regulates the receptors responsible for sensing calcium and endogenous hydrogen sulfide, continuous administration of which causes improved serum levels of hydrogen sulfide and calcium ions in the myocardium. In a different study curcumin loaded nanoparticles were developed using poly lactic-co-glycolic acid-polyvinyl alcohol and studied in streptozotocin induced diabetic cataract model. The researchers concluded improved bioavailability and efficiency [76]. Nanoformulations of berberine has also shown improved bioavailability. Naringenin are flavanones found in citrus fruits and vegetables was found to treat diabetic mice and was also found to improve hematological and immunological parameters of blood. It is reported to have vasorelaxant effect in cardiovascular diseases and hypertension [77]. However, they have poor aqueous solubility and thus have low absorption in the intestine upon oral administration and are prone to rapid elimination from the body [78]. Naringenin encapsulated nanoparticle system has been reported with potent antidiabetic effect with no toxicity in STZ-induced diabetic rats. These polymeric nanoparticles were developed using

biocompatible and biodegradable vehicle for supporting oral administrations [79]. Quercetin is a flavonoid compound having anti-inflammatory and antioxidant activities [80]. Researchers have reported that nanoformulations of quercetin have improved bioavailability profile. Loading of quercetin on poly lactic acid co-glycolic acid is done via emulsion-diffusion evaporation technique to decrease the dose and enhance the bioavailability of quercetin. The researchers conclude an oral bioavailability of 52.3% in rats [81]. Nanorods of Quercetin were also developed and studied on alloxan-induced diabetic rats. The researchers reported that these quercetins loaded nanorods decreases the level of fasting blood glucose in diabetic mice. Quercetin was also found to decrease the generation of lipid peroxidation products [82].

Another novel approach to modify dissolution, absorption, solubility of phytoconstituent is to develop a self-emulsifying drug delivery system. These systems are a mixture of oil, surfactant, co-surfactant and drug substance which is capable of forming nanoemulsion upon reaching the gastrointestinal tract. Self-emulsifying drug deliveries of curcumin have been reported to have potent affect in diabetic neuropathy and relieves neuroinflammation [83]. In a similar study pluronic micelle of curcumin was synthesized and was found to be potent in the treatment of diabetes [84,85]. Curcumin nano emulsions were also prepared and was reported with antihypertensive effect in in vitro study measuring the ACE inhibition and antihypercholesterolemic effect was studied in HMG-CoA reductase assay [86]. Development of nanoemulsions of oleoresin capsaicin have been found to increase expression of PPAR- α , UCP2, and CPT-1 α and decrease decreased adipogenic gene expression which participates in β -oxidation and thermogenesis. Upon administration of the developed nanoemulsion of oleoresin capsaicin was found to drastically lower the adipose tissue mass and final body weight of obese rats which received a high-fat regimen [87]. Bitter ground oil contains α -eleostearic acid which have ROS scavenging and antioxidative effects [88]. Nanoemulsions of bitter ground seed oil was developed to improve the bioavailability of conjugated linolenic acid. The developed formulation was found to reduce the stress state induced by alloxan via antioxidative defence. This research showed the possibility of application of conjugated linolenic acid as a powerful nutraceutical for further applications [89].

Curcumin loaded hydrogels were also developed for its activity in wound healing. Thermos-sensitive hydrogels having curcumin encapsulated in gelatin microspheres

was developed for the treatment of diabetic wounds. Curcumin NPs were found to respond to MMPs which are commonly over-expressed at site of diabetic wounds and also acted as a local delivery system at the wound site [90].

Resveratrol is a polyphenol commonly found in grapes and nuts have antioxidant, anti-inflammatory, analgesic, antiplatelet, neuroprotective, antiaging, cardioprotective effects. It is also found to influence oxidative injury and glucose metabolism [91, 92]. Nanoliposomes of resveratrol were developed for alleviation of diabetes in streptozotocin induced diabetic animals. The liposomes were PEGylated covalently to increase the residence time and plasma half-life. The developed formulation was found to enhance the expression of ROS-inactivating enzymes such as SOD and GSH-Px by extending the release of resveratrol in diabetic pancreatic β TC cells. Resveratrol loaded into nanoliposomes can be exploited in the treatment and protection against type 2 diabetes mellitus [93].

Solid lipid nanoparticles of berberine have been reported with better bioavailability profile in comparison to conventional formulation berberine alone. The researchers also reported remarkable reduction in gaining body weight, fasting glucose level in blood and insulin resistance upon oral administration of berberine encapsulated solid lipid nanoparticles [94]. Myricitrin, a flavanol glycoside was found to prevent reactive oxygen species from causing vein endothelial cell dysfunction [95]. However, the metabolism and bioavailability of flavonoid glycosides are limiting factors in their application. Due to the high polarity of myricitrin, it becomes difficult to cross the membranes [96]. Myricitrin encapsulated solid lipid nanoparticles have shown improved protection against cytotoxicity induced by streptozotocin in β -cells. In addition, solid lipid nanoparticles of myricitrin were also reported with antioxidant and antidiabetic effects in myotube cell of a male mouse and STZ-nicotinamide-induced diabetic model [97].

Novel drug delivery systems of phytochemicals for neurological disorders

Neurological disorders involve the central and peripheral nervous system. It affects the brain, nerve roots, spinal cord, peripheral nerves, cranial nerves, neuromuscular junction, autonomic nervous system, and muscles. These disorders include Parkinson's disease, Huntington's disease, Alzheimer disease and other dementias, epilepsy, neuroinfections, brain tumours etc [98].

Phytochemicals are used by humans since ancient times. They hold a prominent position in Chinese and Traditional system of medicine. A number of phytochemicals have shown prominent activity in neurological disorders. Emergence of nanotechnology has completely evolved the phytochemicals based formulations [99]. Development of nanophytochemicals by using different polymers and modifications of surface properties influences the permeability, solubility, and eventually the bioavailability of the encapsulated medicines. Novel formulations like niosomes, liposomes, cubosome, liposomes, nanospheres, phytosomes etc. have been extensively exploited in formulating phytochemicals for the treatment and management of neurological disorders. In neurological disorders complexity of various neuronal signals and their cross-linking controls the initiation and progression of various neuronal diseases [100]. Hence preparing phytochemicals in combination with nanotechnology provides additional therapeutic advantage within the biological system [99].

Nanoparticles can be synthesized with natural compounds including algae, fungi, bacteria, and plant extracts [101]. For the development of micro-organism-based nanoparticles firstly micro-organisms are grown in the growth medium followed by mixing with metal precursor in solution which is further incubated to form nanoparticles [102]. Plant extract-based nanoparticles are formed by mixing with metal precursor followed by incubation for a definite period of time [103].

In a study by Cheng et al., curcumin loaded nanoparticles were developed which upon oral administration to Tg2576 AD model mice at a dose of 23 mg/kg/week was found to significantly improve memory [104]. In a similar study by Tiwari et al., PLGA nanoparticles loaded with curcumin was found to induce neural stem cell proliferation in vitro and neuronal differentiation in the subventricular zone and hippocampus of adult rats [105]. Sun et al., successfully formulated quercetin nanoparticles and conducted a series of evaluation in which the researchers concluded that the prepared nanoformulation had minimum cytotoxicity and was successful in inhibiting A β 42 fibrillation and reduced A β 42-induced toxicity. The developed formulation showed enhance memory and learning of Alzheimer's disease mice in the Morris water maze test and Novel object recognition test [106]. Quercetin nanoparticles were also developed by Palle and Neerati. In their study the researchers reported prolonged residence time, improved bioavailability and efficacy in rats [107]. Priprem et al. successfully developed nanoquercetin as nanoliposomes and was

found to enhance cognitive functions and anti-inflammatory activity in MCF-10A cells in rat models [108].

Ginsenoside nanoparticles were developed by Aalinkeel et al. The authors in their study reported neuroprotective effect of developed formulation and it was also concluded that the formulation has the ability of crossing the blood brain barrier demonstrated in vitro BBB model [109].

Ramalingam et al. successfully developed solid lipid nanocurcumin and reported enhanced bioavailability of curcumin in the mouse brain with potential pharmacological activity [110,111]. In a similar study by Nazari et al. it was also concluded that nanocurcumin provides a protective effect against the oxidative stress in mice brain [112]. Vitthal et al., developed bacoside loaded solid lipid nanoparticles using tween 80 and stearic acid. *in vitro* drug release studies of developed formulation showed 84.68% drug release from solid lipid nanoparticles [113]. Numerous studies have successfully reported the role of nanoresveratrol in potentially preventing Parkinson's disease enhancing neuronal survival against oxidative stress [114].

Vitamin E-loaded nanoresveratrol emulsion was developed by self-emulsification technique which was further subjected to high-pressure homogenization to make resveratrol available to the brain leading to reduction of the oxidative stress of Parkinson's disease [114]. Nanolycopene was developed by nanoemulsion technique was found to enhance bioaccessibility and *in vitro* antioxidant activity [115]. Nanolycopene was also formulated by exploiting nanostructured lipid carrier technique was found to lessen the degradation and showed improved *in vitro* antioxidant activity [116]. These studies support the theory that lycopene can be stabilized by various techniques and make them available for extended period of time to protect against oxidative stress leading to Parkinson's disease.

Novel drug delivery systems of phytochemicals for the management of cancer

Cancer is one of the leading cause of mortalities around the world and is expected to claim about 13.1 million lives every year by 2030 [117]. Lung cancer, breast cancer, prostate cancer, liver cancer, colon and rectal cancer, skin cancer, pancreatic cancer are some of the most common types of cancers [118]. Cancer can affect any age group or occur at any stage of life. Early detection and treatment of cancer improves survival rate of the patients. Phytochemicals have shown immense potential in the management, maintenance, treatment,

and prevention of many diseases especially cancer [119]. However, technical glitches like poor solubility, low penetration into cells, hepatic disposition, narrow therapeutic index, and quick uptake by normal tissues hinders their routine application. Phytochemicals as therapeutic agents may have unfavourable pharmacokinetic parameters like short half-life and rapid clearance rate. Application of nanotechnology in designing phytochemicals based formulations is revolutionizing their wholesome applications [120]. Thus, nanomedicines could provide an interesting platform to overcome the limitations of phytochemicals by improving solubility, enhancing bioavailability, providing target specific approach, better cellular uptake, reduction in dosing and by achieving steady-state therapeutic concentration of the phytochemicals over an extended period. They may additionally benefit by providing blood stability, multifunctionality and anticancer activity [121]. Nanophytochemicals provided Enhanced permeability and retention (EPR) effect in tumour-targeting [Maeda et al. 2013]. Lipid based nanomedicines, such as solid lipid nanoparticles (SLNs), liposomes, lipid micelles nanostructured lipid carriers (NLCs) and Polymer-based nanomedicines, such as polymeric nanoparticles, polymeric micelles, polymer drug conjugates and dendrimers have shown some promising results for use in anticancer drug delivery [122].

Mullauer et al. successfully formulated betulinic acid encapsulated liposomes which was found to reduce growth of colon and lung cancer in female athymic nude Foxn1 mice. The researchers concluded that the developed formulation showed more than 50% reduction in tumour growth in nude mice xenografted with human lung cancer cell line (A549) and human colon cancer cell line (SW480) compared to free BA, thus supporting claims of improved survival rate with no adverse systemic toxicity [123]. Epigallocatechin-3-gallate loaded nanoliposomes were developed by de Pace et al. and was found to improve the efficacy against MCF-7 breast cancer cells. The developed EGCG-nanoliposomes significantly improved EGCG stability and enhanced sustained release profile of EGCG. EGCG-nanoliposomes was reported with a 9-fold increase in cellular uptake of EGCG by MCF-7 breast cancer cells in comparison to free EGCG. Further, EGCG-nanoliposomes showed significantly improved antitumor activity against MCF-7 breast cancer cells in comparison to free EGCG [de Pace et al. 2013]. In another research Peanut agglutinin (PNA) modified vinblastine (VINB) encapsulated cationic liposomes were fabricated. The developed formulation was found to exhibit improved cellular uptake of VINB in Lewis

lung cancer cells (LLT cells) in comparison to VINB-liposomes [124].

Cucurbitacin B loaded solid lipid nanoparticles (Cu B-SLN) were formulated by Hu et al. and was successfully studied for treatment of hepatic carcinoma. The developed Cu B-SLN were found to exhibit enhanced cellular uptake of cucurbitacin B in human hepatic carcinoma (HepG2) cells in comparison to free Cu B solution. Cu B-SLN showed better reduction in IC50 value in HepG2 cancer cells. The researchers concluded a 1.94-fold increase in targeting efficiency during in vivo anticancer studies [125]. In a similar study Zhu et al. developed podophyllotoxin (PPT) encapsulated solid lipid nanoparticles (PPT-SLNs) and was found to enhance invitro anticancer efficacy of PPT against HeLa human cervical cancer cells and 293 T human embryonic kidney cells. PPT-SLNs was found to improve cytotoxicity towards HeLa and 293 T cells in comparison to free PPT and were also reported to be less toxic to normal cells [126]. In a similar attempt PEG conjugated solid lipid nanoparticles of noscapine (NosPEG-SLNs) were formulated and was reported to exhibit a 2-fold reduction in IC50 value in comparison to free Nos against U87 glioblastoma cells [127]. Emodin encapsulated solid lipid nanoparticles (E-SLN) were developed by Chen et al. and was concluded to enhance the efficacy of emodin against breast cancer with significant cytotoxicity against human hepatoma HepG2 cells and human breast cancer MCF-7 cells in comparison to free emodin solution. The developed formulation was also reported with no major toxicity to normal cells [128].

Curcumin (CUR)-loaded nanostructured lipid carriers (FA-CUR-NLCs) were developed by Lin et al. and was studied for the possible treatment of breast cancer [129]. The researchers concluded that FACUR-NLCs exhibited initial burst release which was followed by sustained release of drug for up to 60 h. the developed formulation was found to have 3.5 and 10.4- fold reduction in IC50 value compared to CUR-NLCs and free CUR respectively when studied in MCF-7 human breast cancer cell line [129]. Isoliquiritigenin encapsulated nanostructured lipid carriers (ISL-NLCs) were developed by Zhang and associates and was studied for its possible effect in the treatment of liver cancer. In their study the researchers concluded that the developed formulation exhibited prominent tumour inhibition rate in comparison to free Isoliquiritigenin in S180 and H22 hepatocellular carcinoma in female Kunming mice. Apart from that in-vivo biodistribution study in H22-bearing mice of ISL-NLCs showed 2.5-fold higher concentration of Isoliquiritigenin compared

to Isoliquiritigenin suspension [130]. Carbone et al. formulated ferulic acid encapsulated nanostructured lipid carriers (FA-NLCs) and was studied for its possible application in the treatment of glioblastoma. The study concluded that ferulic acid encapsulated nanostructured lipid carriers exhibited initial burst release which is followed by sustained release of ferulic acid thus supporting its enhanced anticancer activity against U87MG glioblastoma cell lines in comparison to free ferulic acid [131]. Zerumbone is a terpenoid obtained from several plant species of the Zingiberaceae family and possess pharmacological activities like anticancer activity in lung cancer, blood cancer, colon cancer, cervical cancer, breast cancer, and skin cancer [132]. Zerumbone encapsulated nanostructured lipid carriers (ZER-NLCs) were developed by Rahman et al. and was studied for potential activity in the treatment of leukaemia. The researchers concluded that zerumbone encapsulated nanostructured lipid carriers displayed controlled release of zerumbone following zero order kinetics during invitro drug release studies. In-vitro cytotoxicity study was conducted exploiting MTT assay in human T-cell acute lymphoblastic leukaemia (Jurkat) cells demonstrated appreciable lowering of IC50 by zerumbone encapsulated nanostructured lipid carriers in comparison to free zerumbone solution after treating for 72 h. These findings strongly suggest that nanostructured lipid carriers have potential to provide a sustained release drug nanocarrier system for the effective management of cancer [133].

Quercetin encapsulated polyethylene glycol (PEG)-derivatised phosphatidylethanolamine (PE) based lipidic nanomicelles (QT-PEG-nanomicelles) were successfully developed by Tan et al. and was studied for the potential activity in the treatment of lung cancer. The researchers concluded that the formulated quercetin encapsulated polyethylene glycol based lipidic nanomicelles exhibited improved invitro cytotoxicity against A549 lung carcinoma cells and in vivo cytotoxicity in female Rag-2 M mice bearing A549 xenograft [134]. In a similar study Apigenin encapsulated phospholipid and D-a-tocopheryl polyethylene glycol succinate-based lipid micelles (TPGS-Ap-Ph-micelles) were developed which was found to exhibit 2.4-times improved intestinal absorption compared to free apigenin solution [135].

Yang et al. successfully formulated camptothecin loaded biotinF127-PLA block co-polymeric nanoparticles and studied the same for the effective treatment of hepatocellular carcinoma [136]. Targeting of biotin receptor by the developed camptothecin nanoparticles was found to exhibit an initial burst

release which was followed by sustained release of camptothecin. The developed formulation was studied for its anti-tumor efficacy against H22 hepatocellular carcinoma cells [137]. These studies confirmed significantly higher in-vitro antitumor efficacy of developed formulation in comparison to non-targeted camptothecin formulations [136]. Honokiol loaded hydroxypropyl- β -cyclodextrin conjugated pectin nanoparticles were developed by Zhang et al. and was studied for its potential activity in the treatment of hepatocellular carcinoma. The developed formulation was found to exhibit significantly higher uptake of honokiol via asialoglycoprotein receptor mediated endocytosis into HepG2 cells in comparison to free honokiol which was attributed to the presence of cyclodextrin as a solubility enhancer. Further, the developed formulation was found to exhibit improved apoptosis and in-vitro cytotoxicity against HepG2 cells in comparison to free honokiol [138].

Curcumin loaded polymeric micelles of poloxamer 407/TPGS was successfully formulated by Saxena and Hussain and was studied for its potential activity in the treatment of multidrug resistant ovarian cancer [139,140]. The researchers concluded in their study that the developed polymeric micelles of curcumin showed sustained release for more than 9 days. It was also reported that the curcumin loaded micelles exhibit improved cellular uptake and about 3-times more cytotoxicity against multidrug resistant ovarian cancer cell lines (NCI/ADR-RES cells) in comparison to free curcumin [140]. In a similar attempt, triptolide loaded polymeric micelles were developed and was found to exhibit enhanced membrane damage, proliferation and inhibition of tumour cell growth in HT29 and Jurkat cancer cells at a very low concentration in comparison to free triptolide solution [141]. β -Lapachone loaded PEG-PLA polymeric micelles were developed by Balcano et al. and was investigate for their potential activity on NAD(P)H:quinone oxidoreductase 1 (NQO1) overexpressing tumours. In vitro cytotoxicity study was performed on MDA-MB-231 breast cancer cells, NQO1-null (NQO1) H596 lung cancer cells, DU-145 prostate cancer cells and NQO1-overexpressing (NQO1 β). It was concluded that the developed formulation showed enhanced anticancer activity towards NQO1 β overexpressing cancer cells via receptor mediated endocytosis of β -lapachone encapsulated micelles in comparison to NQO1-cancer cells [142]. In a similar study apigenin encapsulated polymeric micelles were developed and was further studied and confirmed enhanced cytotoxicity on MCF7 human breast cancer cell line [143].

Dendrimers loaded with folic acid in conjugation with ursolic acid were also developed and was shown to exhibit enhanced efficacy against folate receptor overexpressed tumour [144]. The developed dendrimers exhibited improved cellular uptake of ursolic acid in folate receptor over-expressing HeLa cells in comparison to lone ursolic acid dendrimers and free ursolic acid and also resulted in 2.2 times reduction in IC₅₀ in HeLa cells [144]. In a similar attempt, folate receptor targeted dendrimer/ combretastatin A4 inclusion complexes as multifunctional modality was developed by Zhang et al. and was studied for their potential activity in the treatment of cancer. Their results conclude that the developed targeted combretastatin A4 entrapped dendrimer showed enhanced aqueous solubility of the hydrophobic combretastatin A4 and was able to release combretastatin A4 in a controlled and sustained manner [145].

Curcumin encapsulated magnetic nanoparticles was developed by Yallapu et al. and was studied for their potential application in the treatment of pancreatic cancer. The developed formulation exhibited improved cellular uptake and cytotoxicity in dose dependent manner in Panc-1 pancreatic cancer cells in comparison to free curcumin. It was also concluded that the developed curcumin loaded magnetic nanoparticles improved serum bioavailability of curcumin and eventually the survival time of mice [146]. Artemisinin loaded magnetic nanoparticle of iron and silver were developed and was found to exhibit improved cellular uptake and enhanced cytotoxicity in HeLa cells due to complete internalization and localization into the acidic compartments of lysosomes and endosomes and releasing Fe²⁺ ions which converts artemisinin into toxic products responsible for its cytotoxic activity against cancer cells [147].

Gold nanoparticles loaded with epigallocatechin-3-gallate were developed by Chen et al. The authors concluded that the developed formulation exhibited enhanced efficacy against B16F10 melanoma cells. The efficacy against B16F10 murine melanoma cells of the developed formulation was found to be 4.91 times more in comparison to free epigallocatechin-3-gallate. The researchers concluded that the enhanced efficacy was attributed to mitochondrial pathway-mediated apoptosis of melanoma cells. Further, the developed gold nanoparticles were found to be 1.66 times more potent than epigallocatechin-3-gallate in inhibiting tumour growth in murine melanoma model [147]. In a similar attempt gold nanoparticle loaded with kaempferol were developed and was found to exhibit significantly higher

induction of apoptosis and strong dose and time dependent reduction in viability of MCF-7 breast cancer cells in comparison to free Kaempferol [148].

Novel drug delivery systems of phytomedicines for viral diseases

Viral infections take millions of lives every year. Some of most hostile viral infections are AIDS (acquired immunodeficiency syndrome), influenza, Ebola, and SARS (severe acute respiratory syndrome), coronaviruses [149]. Mortality due to viral infections is increasing at an alarming rate. Conventional antiviral drugs like interferon and ribavirin are found to be effective during in vitro studies against most viruses' but are mostly ineffective in patients. More than 90 antiviral agents are currently available in the market [150] which only treats some selected viruses like VZV (varicella zoster virus), HSV (herpes simplex virus), HIV (human immunodeficiency virus), hCMV (human cytomegalovirus), hepatitis viruses and the influenza viruses. Thus, phytomedicines may provide an attractive alternative for treating viral diseases. Phytochemicals are isolated, purified, and identified from the crude extracts of flavonoids, alkaloids, proteins, various glycosides and terpenes [151]. Plants have different chemical compounds which possess antiviral activity for example rutin, a flavonoid glycoside was found to be effective against parainfluenza-3 virus, HSV-1 and -2 and avian influenza virus [149]. Introducing pharmaceutical nanotechnology into phytomedicines offers promising alternative. Nanotechnology allows delivery of sparingly soluble phytochemicals with improved pharmacokinetic and clinical outcomes. Novel technologies like developing microspheres, nanoparticles, phytosomes, hydrogels, ethosomes, transferosomes, self-nanoemulsifying drug delivery systems (SNEDDS) and self-microemulsifying drug delivery systems (SMEDDS), is long been used for delivering conventional antiviral drugs and has potential to be exploited for the effective delivery of phytochemical drug formulations in order to improve solubility, absorption, bioavailability, safety and toxicity profiles and eventually leading to enhanced antiviral activity.

Qian et al. successfully formulated myricetin loaded self-nano-emulsifying drug delivery system and studied its potential antiviral activity in Caco-2 cancer cells. The developed formulation exhibited enhanced solubility and oral bioavailability. In vitro drug release profile of myricetin loaded self-nano-emulsifying drug delivery system showed dissolution of over 90% after 1 min. The

developed formulation achieved higher plasma myricetin concentration [152].

Oleanolic acid is a pentacyclic triterpenoid is found to have poor solubility in water and extremely low systemic bioavailability. To overcome these limitations, oleanolic acid loaded self-micro-emulsifying drug delivery systems using 35% Cremophor EL as surfactant, 50% ethyl oleate as oil base and 15% alcohol as co-surfactant were developed [153]. The researchers concluded that the developed formulation demonstrated sustained release behaviour during in vitro studies. Systemic rat bioavailability was also found to be significantly improved in the developed formulations than the marketed formulation of oleanolic acid. Improvement in the oral bioavailability of the drug was attributed to enhanced solubility due to emulsification and improved permeability due to small particle sizes [153].

Kim et al. developed apigenin loaded water-in-oil-in-water emulsions and reported improved solubility and enhanced bioavailability of apigenin. The developed formulation showed enhanced stability in terms of zeta potential and particle size during pharmacokinetic tests in animal model. Apigenin loaded water-in-oil emulsion showed 9-times higher plasma concentration in comparison to free apigenin suspension [154].

Zhang et al. developed baicalin loaded micelles using carrier sodium taurocholate and pluronic P123 copolymer to achieve enhanced oral absorption and to overcome poor solubility and low permeability of baicalin. The developed baicalin-loaded mixed micelles showed sustained release profile during in vitro drug release studies under different pH conditions. The researchers also reported improved stability of the formulation. During the in vitro uptake studies on Caco-2 cell line suggested enhanced internalization of baicalin from baicalin-loaded mixed micelles. It was also concluded that baicalin encapsulated ST-P123-mixed micelles achieved enhanced oral bioavailability [155].

In a similar attempt honokiol loaded inclusion complex of sulfobutyl ether- β -cyclodextrin was developed. The formulation demonstrated improved solubility and bioavailability of the loaded phytomedicine [156]. The solubility was found to be directly proportional to the growing levels of cyclodextrin when studied in the phase solubility experiment. The developed formulation also demonstrated enhanced released rate than either physical mixture of honokiol/cyclodextrin or honokiol alone. During the pharmacokinetic studies of the inclusion complex, AUC and C_{max} were found to be 1.58

and 1.23-folds higher in comparison to honokiol suspension, respectively. The body clearance was also 3-folds higher in honokiol suspension in comparison to complexed honokiol [156].

Andrographolide, labdane diterpenoid is a highly bitter and poorly aqueous soluble phytochemistry. It is also very unstable in strong acidic and basic environments. These characteristics are responsible for their low absorption and poor bioavailability. In an attempt to overcome the before mentioned drawbacks andrographolide loaded PLGA (poly(lactic-co-glycolic acid)) microspheres were developed [157]. The developed andrographolide microsphere exhibited sustained release profile over 9 days during in vitro studies, with just 14% andrographolide released during the first 8 hours which is attributed to the low drug density at the surface of the developed microspheres, thus allowing enhanced oral bioavailability of 67.5%. The authors also demonstrated correlation between in vitro drug release and in vivo absorption, indicating that the in vitro assay may act as a good predicting tool for in vivo drug absorption [157].

Novel drug delivery systems of phytochemicals for inflammatory diseases

Tissue injuries by stress, radiation, genetic distortion or microbial or viral infection may trigger physiological response of the body in the form of inflammation. Inflammations can be of acute or chronic nature. Acute response includes high capillary permeability, local vasodilation, accumulation of blood proteins and fluid in the interstitial spaces, release of cytokines, histamines lymphokines like inflammatory mediators and migration of neutrophils out of the capillaries [158]. Repetitive local inflammation due to increased production of cytokines like tumor necrosis factor (TNF)- α and interleukin-1 β , tissue micro-damage and abnormal microbial sensing (as in inflammatory bowel disease) leads to delay in switching off physiological responses eventually leading to auto-immune disorders [159]. If the condition is not resolved it leads to subacute/chronic inflammation which is characterized by immunopathological changes like overexpression of pro-inflammatory genes, infiltration of inflammatory cells, loss of barrier function and dysregulation of cellular signaling. Such chronic inflammatory conditions may lead to the onset of various diseases such as diabetes [160,161], neurodegenerative diseases, asthma, periodontal diseases cardiovascular disease, arthritis cancer, obesity [162]. Treatment strategies include steroid and non-steroidal medications. However, they come with the side-effects like anemia, gastric irritation, renal failure, ulceration, headache,

bleeding, hemolytic asthma, angioedema, hepatic failure, pruritus and skin rashes [163]. During recent times, phytochemicals have gained immense attention due to their safer toxicological profiles in comparison to synthetic drugs for the treatment of inflammatory disease [164]. Phytochemicals have been found to be potent in the treatment of skin inflammation, Alzheimer disease, obesity mediated inflammation, diabetes and inflammatory bowel disease [165,166]. However, despite promising biological activities these phytochemicals come with the drawback of poor stability, low solubility, short biological half-life, and quick elimination from the body. Nanotechnology has already been employed in tissue engineering and traditional drug delivery systems, nanotechnology can be applied to phytochemicals based systems in order to enhance bioavailability, target site specificity and reduced toxicity [167].

Barras et al. developed quercetin encapsulated lipid-coated nanocapsules and reported that the developed formulation exhibited enhanced solubility, increased stability and no degradation was found over a period of time [168]. In a similar study, Pool et al. successfully developed quercetin-loaded nanocapsules and reported potentially enhanced antioxidant activity against peroxy radical-induced lipid peroxidation which eventually results in effective anti-inflammatory therapy [169].

Chakraborty et al. developed quercetin loaded poly(lactic-co-glycolic acid) nanoparticles and studied it for its potential activity on alcohol induced gastric ulcer rat model [170]. The researchers concluded that the developed formulation prevented 90% of this inflammation in comparison to only 20% of free quercetin [170]. Singh and Pai developed resveratrol based nano vectors and demonstrated sustained release of trans-resveratrol from orally administered poly(lactic-co-glycolic acid) nanoparticles with drug encapsulation efficiency of more than 78% [171].

Wang et al. developed curcumin loaded oil-in-water nanoemulsion and reported enhanced anti-inflammatory activity of the developed formulation [172]. Takahashi et al. developed curcumin encapsulated liposomes using lecithin and reported enhanced bioavailability, faster pharmacokinetics and improved absorption of the drug in rats [173].

Esposito et al. successfully encapsulated phytocannabinoids in nanostructured lipid carriers [174] and reported enhanced bioavailability and drug encapsulation efficiency [174]. In a similar attempt Lobato et al. developed cannabinoid derivatives loaded

lipid nanoparticles and studied its potential activity in combating chronic pain [175]. The formulation was developed using solvent-emulsion evaporation technique and was found to possess improved encapsulation efficiency, enhanced bioavailability and targeted effect.

Rossi et al. successfully formulation phytosterols based colloidal particles by exploiting antisolvent precipitation technique. The resulting phytosterol based colloidal particles was found to have improved stability and enhanced bioavailability [176]. In a similar attempt, Turk et al. developed phytosterol based sub-micron particle suspension. The researchers concluded in their study that the developed formulation was found to be stable during long term stability studied and showed very little particle growth over a period of 12 months and also exhibited improved bioavailability [177]. Bizzarro et al. developed basil oil and cumin encapsulated polyamide capsules which can potentially release their encapsulated oil under UV-light irradiation [178].

Butnariu and Giuchici developed aqueous propolis and lycopene loaded nanoemulsions which was demonstrated to have protective activity against acute UV-A-induced inflammation on rat paw. The researchers reported enhanced therapeutic effect in comparison to standard suspension. In a recent attempt, stable lycopene encapsulated solid lipid nanoparticles based on orange wax or myristic acid was developed with improved chemical stability of lycopene entrapped in the solid lipid nanoparticle system [179].

Novel drug delivery systems of phytomedicines in wound healing

Wound healing involves the processes to restore the integrity of skin through a regulated and sequential cellular and biochemical phenomenon [180]. Management of wound and the efficacy of healing process depends on the wound dressing materials. Many studies have supported the application of traditional wound healing therapies [181]. Phytochemicals such as phenolic compounds, flavonoids, alkaloids, terpenoids, essential oils, fatty acids can act as potent and promising agents in wound healing process [182]. In the management of wound healing phytomedicines provide the advantages of efficacy, bioavailability, limited side-effects and cost effectiveness [183]. Beside the advantages of phytomedicines in wound healing, a promising way to promote its efficacy is to expose them to novel nanotechnological techniques. Being in the nano-size range, nanomaterials provide enhanced surface area to volume ratio. Phytomedicines can be

used directly as medicaments to improve the rate of wound healing process or may also act as drug carriers for delivery of other therapeutic agents [184].

Cellulose acetate based nanostructured wound dressing developed by co-electrospinning technique using emodin biopolymer with gelatin polyester urethane, poly (ϵ -caprolactone), polyurethane, zein and polylactic acid [185]. Cellulose acetate loaded with polyhexamethylene biguanide and polyether urethane demonstrated enhanced physical and mechanical property, antibacterial activity, air permeability, moisture retention antibacterial property thus accelerating the wound healing process. Cellulose acetate in nanofibrous membrane significantly increases the water uptake and creates a moist environment around wound improved adhesion to the rat skin fibroblast and supported the rapid regeneration of epidermal layer [186].

Catharanthus roseus leaf extract loaded into silver nanoparticles was developed and their in vivo studies was reported to control fungal and bacterial growth, demonstrated closing of wound, and significantly reduced the wound site [187]. Endophytic fungus of *O. chinensis* when exploited for the green synthesis of silver nanoparticles was found to effectively treat the infected wounds developed on the Sprague Dawley rats [188]. The developed formulation was found to inhibit various bacterial strains by metabolizing proteins. The formulation improved wound contraction rate, decreased the bacterial count on the infected site, accelerated wound healing, and effectively re-epithelialized the epidermis [188].

Cassia auriculata L.-mediated silver nanoparticles were found to be effective against incision as well as excision wound models of Wistar albino rats. Although there is documented literature in support of wound healing activity of Cassia auriculata extract alone, however, Cassia auriculata silver nanoparticles were found to exhibit improved in wound healing process in comparison to the free extract alone and also to Povidone Iodine ointment. Nanoparticles were also reported to be more effective on accelerating the excision wound contraction [189].

Essential oil of Eucalyptus globulus was nanosized by exploiting nano-emulsification technique which enhanced their antibacterial activity. The high potency and enhanced wound healing ability could be attributed to the presence of high amount of eucalyptol which are highly active compounds and are capable of penetrating into transdermal layer [190]. In a similar study tragacanth gum nanoemulsions loaded with *A. vera*

extract was found to demonstrate excellent wound healing results during in vitro and in vivo studies which was linked to the potential of *A. vera* in modulation of proteases [191]. The loading of active phytochemicals into nanoemulsions has provided a new provided for controlled drug delivery. Encapsulation of phytoconstituents into nanoemulsions facilitates their penetration into the dermal layers and provides a dispersed oil droplet phase in order to improve their solubility [192].

Nanoliposomes can be exploited to improve the solubility and efficacy of sparingly soluble phytomedicines. Nanoliposomes are colloidal structures composed of phospholipid bilayers enclosing an aqueous compartment(s) and have the ability to enhance bioavailability through sustained transdermal delivery of phytomedicines, enhanced skin permeability, retention time and overcome the possible drug overdose and related toxicity [193]. Polyethylene glycol has been used successfully in the development of phytomedicines based liposomal systems in order to enhance their dermal delivery. Curcumin loaded PEGnanoliposomes

was found to improve its anti-inflammatory activity, enhanced the permeation rate into the dermal layers, and accelerated the wound contraction [194].

Discussion

The application of nanotechnology has enormously increased in the last two decades. Its application is now not limited to pharmaceuticals but has also reached to food and nutraceuticals [195,196]. In this extensive review we have discussed various phytochemicals which had been successfully encapsulated into nanoparticulate system [197-199]. Nanotechnology are also being exploited for the development of not only oral products [200] but also parenteral delivery systems [201]. However, the toxicity concerns associated with nanotechnological products cannot be denied and need special consideration during and after development of a formulation [202,203]. Nanotherapeutics have been successfully applied in neurological disorders, metabolic disorders and for the treatment of cancer [204-206]. Here we enlist the nanophytomedicines in the treatment of major diseases (**Table 1**).

Table 1: List of nanophytomedicines in the treatment of major diseases.

Disease	Phyto-constituents	Nanocarrier	Conclusion	References
Neurological Disorder	Curcumin	Polymeric nanoparticle	ApoE3-C-PBCA was reported to provided advantage in the treatment of beta amyloid induced cytotoxicity in AD	Mulik et al. [207]
	Coumarin-6/H102	Polymeric nanoparticle	TQNP was reported to be an effective nanodevice for the accurate delivery for biotechnological drugs to treat AD	Zheng et al. [208]
	Nicotine	Polymeric nanoparticle	Nano formulation of nicotine was found to improve its neuroprotective efficacy by enhancing its bioavailability and by subsequently modulating the indicators of apoptosis and oxidative stress	Tiwari et al. [209]
	Quercetin and rosmarinic acid	Liposome	Researchers concluded that the surface functionalization of liposomes using PA and ApoE can provide a promising approach for effectively crossing the BBB and delivering quercetin and rosmarinic acid to the brain for effective management of Aβ1-42-induced neurotoxicity.	Kuo et al. [210].
	α-mangostin	Liposome	Tf(α-M) liposome was found to be effectively improve the brain	Chen et al. [211]

			delivery of α -M and hence it could be a potential carrier of α -M against AD	
	Piperine	Solid lipid nanoparticle	SLN of piperine was found to show therapeutic effects in AD <i>via</i> reducing the oxidative stress and the cholinergic degradation at 2 mg/kg dose equivalent.	Yusuf et al. [212]
	Curcumin	Polymeric nanoparticle	Nanoparticles of curcumin was found to be effective in crossing the BBB and hence could be an effective approach in the treatment of AD	Del Prado-Audelo et al. [213]
	Berberine	Multi-walled carbon nanotubes	The study shows significant potential of polysorbate/phospholipid coated MWCNTs of BRB for the holistic management of AD	Lohan et al. [214]
	Osmotin	Magnetic nanoparticle	Magnetic nanoparticles of osmotin were found to improved brain transportation and eventually treatment of AD	Amin et al. [215]
Cancer	Silybylin	Phytosomes	The formulated phytosomes was found to decrease fat accumulation and oxidative imbalance.	Vecchione et al. [216]
	Diospyrin	Liposomes	Diospyrin liposomes showed antitumor activity in vivo and cancer cell lines of human in vitro. Encapsulated into lysosome was reported to reduce the toxicity	Hazra et al. [217]
	Piperine	Nanoparticles	Piperine liposome complex formulation was found to be stable for 3 weeks after storing it at 4°C	Pentak [218]
	Matrine	Ethosomes	Ethosome-matrine complex was reported to increase per cutaneous permeation and was found to assist in the improvement of anti-inflammatory effect	Bhokare et al. [219]
	Docetaxel	Emulsions	Microemulsions containing docetaxel was reported with increased bioavailability of the drug with improved solubility	Cui et al. [220]
	Quercetin	Phytosomes	Quercetin-loaded phytosome nanoparticles (QP) was reported with improved encapsulation efficiency and bioavailability.	El-Fattah et al. [221]
	Berberine	Nanoparticles	Nanoparticle berberine carrier with a heparin shell as an in vitro drug carrier method controlled the berberine release, which interacted in intercellular space at the infection site precisely	Chang et al. [222]

Metabolic Disorder	Diabetic neuropathy	Curcumin	SNEDDS	Curcumin loaded SNEDDS was found to decrease TNF- α and IL-6	Joshi et al. [223]
		Quercetin	(QUE/P) NP	Quercetin nanoparticle was found to downregulate ICAM-1 expression	Tong et al. [224]
	Diabetes	Berberine	Solid lipid nanoparticles	Berberine solid lipid nanoparticles was found to decrease body weight, fasting blood glucose levels and HOMA-IR	Xue et al. [225]
		Naringenin	Alginate-coated chitosan core-shell	Naringenin based alginate coated chitosan core shell was found to provide better toxic effect with low to no side-effects	Shi et al. [226]
		Quercetin	pH sensitive chitosan-alginate core-shell	Quercetin based pH sensitive chitosan alginate core shell was found to decrease serum AST, ALT and ALP levels	Mukhopadhyay et al. [227]
			PLGA NPs	Quercetin loaded PLGA nanoparticles was found to increase CAT and SOD levels with lower the drug dose	Chitkara et al. [228]
		Gymnemic acid	Nanosuspension	Gymnemic acid loaded nanosuspension was found to decrease the blood glucose levels	Ravichandran et al. [229]
		Baicalin	Nanostructured lipid carriers	Baicalin nanostructured lipid carriers was found to decrease the FBS, HbA1c, and TG levels	Shi et al., [226]
		Resveratrol	Nanoliposomes	Resveratrol nanoliposomes was found to increase the ROS-inactivating enzymes including GSH-Px and SOD	Yücel et al. [230]
		Myricitrin	Solid lipid nanoparticles	Myricitrin SLNs was found to improve the SOD level, muscle and myotube glycogen content, Glut4 gene expression in skeletal muscle and C2C12 cells, Bcl-2 gene expression, Bax to Bcl-2 ratio of myotubes	Ahangarpour et al. [231]
Stevioside	Pluronic-F-68 copolymer-based PLA nanoparticles	Stevioside loaded pluronic-F-68 copolymer based PLA nanoparticles was found to increase intestinal absorption, bioavailability,	Barwal et al. [232]		

				biocompatibility and controlled release	
		α -eleostearic	Bitter Gourd Seed Oil Nanoemulsion	α -eleostearic loaded bitter gourd seed oil nanoemulsion was found to increase PPAR- γ GPx, SOD, and CAT	Paul et al. [233]
	Hypertension	Curcumin	Nanoemulsion	Curcumin nanoemulsion was found to inhibit of HMGR along with ACE	Rachmawati et al. [234]

Future Prospect and Conclusion

Nano-phytomedicines are attracting researchers from around the globe and provides a potential alternative in the effective treatment and management of metabolic disorder, cardiovascular diseases, neurological disorders, cancer, viral diseases, inflammatory diseases, wound healing etc. A number of phytochemicals designed into novel drug delivery system have been found to be promising in this regard. Tailoring phytochemicals into nanomedicines have the potential to improve solubility, stability, bioavailability, bioactivity, sustained and targeted delivery with decreasing their toxicity profile.

The development of phytomedicines in association with nanotechnology is being carried out at different levels of clinical research. It is the need of the hour to develop novel delivery system which can deliver phytomedicines at the targeted site with effectively diminishing its side effects. As a future prospect, the development of phytomedicines for the effective management and treatment of various clinical and medical complications is a vast area that needs special consideration. Phytomedicines loaded nanotechnology has established itself as an attractive therapeutic and pharmacological approach in the medical and pharmaceutical field to enhance the health care system. It can be anticipated that the valuable and effective relevance of phytomedicines with nanocarrier systems will positively influence the significance of existing system of drug delivery.

Consent for Publication

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Conflict of Interest

The author declares no conflict of interest, financial or otherwise.

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